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(54) Title: ANDROGEN GLYCOSIDES AND ANDROGENIC ACTIVITY THEREOF		
(57) Abstract Androgen glycosides provide free, circulatory androgen on oral administration as they are subject to less, first pass breakdown by the liver.		

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ANDROGEN GLYCOSIDES AND ANDROGENIC ACTIVITY THEREOF

The present invention relates to androgen derivatives and their use in therapy.

Testosterone, an anabolic androgenic C19 steroid with a hydroxy group in position 17, is the principal male sex hormone. It is either synthesised from cholesterol and secreted by the Leydig cells in the testes or formed in the adrenal cortex [Ganong, Chapter 23 in *Review of Medical Physiology*, (1979), pp. 336-339]. Testosterone is found in androgen-dependent target tissues, such as the testes, kidneys, skin, liver and prostate, where it is converted to 5 α -dihydrotestosterone (DHT) by 5 α -reductase. DHT is required for male sexual differentiation. Testosterone is also found in the brain where it is converted to oestradiol by aromatase. This conversion permits mediation of androgenic effects which include gonadotropin secretion regulation, sexual function and protein synthesis [Handelsman, "Testosterone and Other Androgens: Physiology, Pharmacology, and Therapeutic Use," in *Endocrinology - Volume 3*, Ed's DeGroot *et al.*, (1995), pp. 2351-2361].

Testosterone is also found in skeletal muscle. However, testosterone is not converted to DHT in skeletal muscle tissue, due to low 5 α -reductase activity (Handelsman, *supra*). According to Catlin, anabolic androgenic steroids, such as testosterone, increase the width and cross-sectional area of muscle fibres by increasing the myofilament and myofibre number [Catlin, "Anabolic Steroids," in *Endocrinology - Volume 3*, Ed's DeGroot *et al.* (1995), pp. 2362-2376]. In hypogonadal men, this results in an increase in lean body mass and body weight, and a decrease in body fat [Handelsman, "Testosterone and Other Androgens: Physiology, Pharmacology, and Therapeutic Use," in *Endocrinology - Volume 3*, Ed's DeGroot *et al.* (1995), pp. 2351-2361; Catlin, "Anabolic Steroids," in *Endocrinology - Volume 3*, Ed's DeGroot *et al.* (1995), pp. 2362-2376].

Testosterone and related synthetic androgens are often used in androgen replacement therapy to obtain pharmacological androgenic effects to treat conditions such as hypogonadism. Hypogonadism may be caused by a testosterone deficiency, resulting in manifestations of androgen deficiency, such as ambiguous genitalia, sexual dysfunction, osteoporosis, flushing, delayed puberty, micropallus, anaemia, incidental biochemical

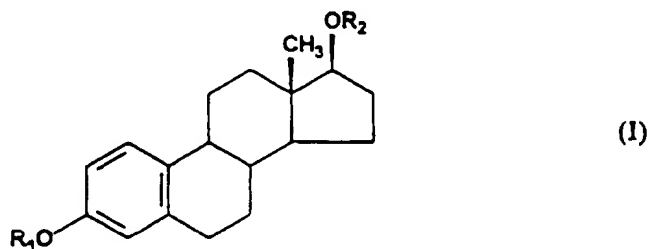
diagnosis or excessive fatigability [Handelsman, "Testosterone and Other Androgens: Physiology, Pharmacology, and Therapeutic Use," in *Endocrinology - Volume 3*, Ed's DeGroot *et al.* (1995), pp. 2351-2361]. Androgen replacement therapy has also been used to treat muscular diseases. However, such treatment generally involves administering orally active 17 α -alkylated androgens which are hepatotoxic [Handelsman, "Testosterone and Other Androgens: Physiology, Pharmacology, and Therapeutic Use," in *Endocrinology - Volume 3*, Ed's DeGroot *et al.* (1995), pp. 2351-2361].

In hypogonadism treatment, androgen replacement therapy often consists of administering testosterone compounds to an individual to maintain testosterone levels for a prolonged period. Testosterone is ineffective, when orally administered, due to poor intestinal absorption and rapid hepatic metabolism [Daggett *et al.*, *Hormone Res.* 9:121-129 (1978)]. Therefore, the effects of testosterone must be obtained by alternative means including administering sublingual methyl testosterone, injecting testosterone or testosterone esters, implanting testosterone, administering oral testosterone derivatives, *e.g.*, fluoxymesterone, or applying testosterone by transdermal means [Bals-Pratsch *et al.*, *Acta Endocrinologica (Copenh)*, 118:7-13 (1988)]. The latter method requires large patches which can be irritating or uncomfortable when applied to the scrotum. In addition, patch application can be inconvenient and is only effective when detailed instructions are followed.

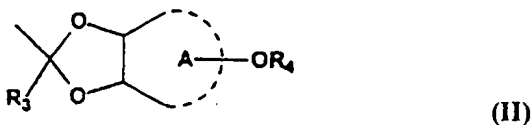
Oral testosterone derivatives include 17 β -esters, 7 α -methyl, 17 α -alkyl or methyl, 19-normethyl and D-homoandrogens [Handelsman, "Testosterone and Other Androgens: Physiology, Pharmacology, and Therapeutic Use," in *Endocrinology - Volume 3*, Ed's DeGroot *et al.* (1995), pp. 2351-2361]. Other known testosterone derivatives include testosterone substituted at the C1 position with methyl, *e.g.*, methenolone and mesterolone. However, these compounds have reduced oral potency. Compounds with substitutions in, and additions to, the A ring, *e.g.*, oxandrolone and stanozolol, are also known (Catlin, *supra*).

Testosterone has also been used in combination with a progestogen to achieve reversible male contraception [Wu *et al.*, *Journal of Clinical Endocrinology and Metabolism* 84(1): 112-122 (Jan. 1999)].

US-A-5.612,317 discloses methods of treating and preventing osteoporosis and alleviating the symptoms of menopause by administering an oestrogen glycoside or oestrogen orthoester glycoside. The compounds have the formula (I):



wherein R_1 and R_2 are independently hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue, or R_1 or R_2 is an orthoester glycoside moiety of the Formula (II):



wherein A represents a glycofuranosyl or glycopyranosyl ring;

R_3 is hydrogen; lower C_{1-4} alkyl; C_{7-10} aralkyl; phenyl or phenyl substituted by chloro, fluoro, bromo, iodo, lower C_{1-4} alkyl or lower C_{1-4} alkoxy; or naphthyl; and

R_4 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue;

with the further proviso that at least one of R_1 and R_2 is either a glycosidic residue or an orthoester glycoside moiety.

Hirotsu and Furuya disclose the biotransformation by cultured tobacco cells of the C-19 steroid testosterone into a variety of steroid glucosides, one of which is testosterone-17-glucoside [Hirotsu and Furuya, *Phytochemistry* 13: 2135-2142 (1974)].

Kocovský *et al.* disclose the synthesis of a variety of steroid glucosides including testosterone-17-glucoside and testosterone-17-glucoside tetraacetate [Kocovský *et al.*, *Coll. Czech. Chem. Commun.* 38:3273-3278 (1978)].

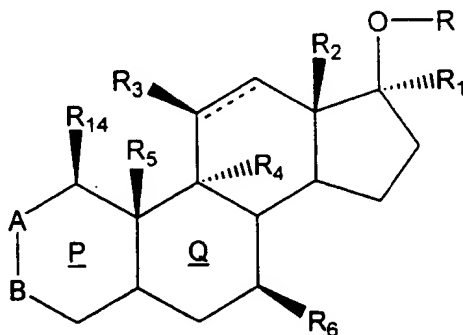
Becker and Galili disclose the synthesis of testosterone-17-glucoside [Becker and Galili, *Tetrahedron Lett.* 33:4775-4778 (1992)].

Vojtišková *et al.* disclose a study on the biological activity of testosterone-17-glucoside in mice [Vojtišková *et al.*, *Int. J. Immunopharmac.* 4: 469-474 (1982)]. This glucoside showed very little activity *in vivo*, and certainly less than testosterone administered by the same route.

It has now, surprisingly, been found that androgen glycosides taken orally are less susceptible to hepatic degradation than the corresponding unglycosylated androgen and are only substantially de-glycosylated after the first passage through the liver, thereby resulting in higher circulatory levels of the androgen. These compounds also appear to be more susceptible to gastric uptake.

Thus, in a first aspect, the present invention provides an androgen glycoside, other than testosterone-17- β -1'- β '-D-glucopyranose.

In an alternative aspect, the present invention provides a compound having the Formula (III):

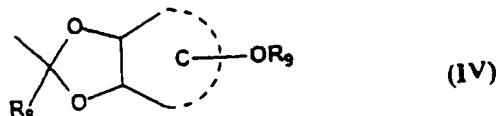


(III)

wherein the dotted line represents a single or double bond;

the rings P and Q are, independently, saturated or partially unsaturated;

R is hydrogen or a straight or branched chain glycosidic residue containing 1 - 20 glycosidic units per residue, or R is an orthoester glycoside moiety of the Formula (IV):



wherein the semi-dotted ring indicated at "C" is a glycofuranosyl or glycopyranosyl ring;

R₈ is hydrogen; C₁₋₄ alkyl; C₇₋₁₀ aralkyl; phenyl; phenyl substituted by chloro, fluoro, bromo, iodo, C₁₋₄ alkyl or C₁₋₄ alkoxy; or is naphthyl;

R₉ is hydrogen or a straight or branched chain glycosidic residue containing 1 - 20 glycoside units;

R₁ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkanoyl or R₁ and R, together with the atoms to which they are attached, form a carbonyl group;

R₂ is hydrogen or C₁₋₄ alkyl;

R₃ is hydrogen or hydroxy;

R₄, where present, is hydrogen or a halogen atom;

R₅, where present, is hydrogen or C₁₋₄ alkyl;

R₆ is hydrogen or C₁₋₄ alkyl;

R₁₄ is hydrogen or C₁₋₄ alkyl;

A is oxygen, $\equiv\text{CH}$, $>\text{C}=\text{CHOH}$, or is the group $>\text{CHR}_{13}$, wherein R₁₃ is hydrogen or a C₁₋₄ alkyl group, or A and B together form an optionally substituted pyrazole or isoxazole ring;

B is a carbonyl group, $\equiv\text{CH}$, $>\text{CH}_2$, $>\text{CHOR}_7$ or $=\text{C}(\text{OR}_7)-$, wherein R₇ is hydrogen or a straight or branched chain glycosidic residue containing 1 - 20 glycoside units, or R₇ is an orthoester glycoside moiety of the Formula (V):



wherein the semi-dotted ring indicated at "D" represents a glycofuranosyl or glycopyranosyl ring;

R₁₀ is hydrogen; C₁₋₄ alkyl; C₇₋₁₀ aralkyl; phenyl; phenyl substituted by chloro, fluoro, bromo, iodo, C₁₋₄ alkyl or C₁₋₄ alkoxy; or is naphthyl; and

R₁₁ is hydrogen or a straight or branched chain glycosidic residue containing 1 - 20 glycoside units;

and esters thereof;

provided that the compound is not an unsubstituted glucoside of testosterone, 5 α -androstane-3 β ,17 β -diol or epiandrosterone, and that, when R is hydrogen, then B is >CHOR₇ or =C(OR₇)-, and R₇ is a glycosidic residue or orthoester glycoside moiety.

It will be appreciated that the rings P and Q are never fully unsaturated, and it is preferred that the core tetracyclical structure corresponds to that of a known androgen. Where substituents are specified herein, these will, generally, preferably be with reference to such a consideration.

In the compounds of Formula (III), when A and B together form a ring, then it is preferred that the ring be a [2,3-d]isoxazole or a [3,2-c]pyrazole ring. Where present, it is preferred that C and D represent glycopyranosyl rings.

In a preferred embodiment R₁₃ is not hydrogen.

Where the compound is an ester, then it is preferred that it is an orthoester glycoside, preferably where at least one glycosidic residue is acylated. Acylation is preferably by a group R₁₂-(C=O)-, wherein R₁₂ is hydrogen, C₁₋₆ alkyl, C₆₋₁₀ substituted or unsubstituted aryl or is C₇₋₁₆ aralkyl. Particularly preferred is where R₁₂ is methyl.

The present invention further provides an androgen glycoside for use in therapy, and may be any compound as defined above, including testosterone glucoside. The therapy is preferably any of those described herein.

Particularly preferred compounds are 17- β -O-(1'- β '-glucopyranosyl)-3-androsterone, 5-androsten-3- β -O-(1'- β '-glucopyranosyl)-17-one and testosterone-17- β -1'- β '-D-glucopyranose.

It will be appreciated that the compounds of the invention are precursors for the free androgen.

The present invention further provides methods for treating androgen deficiency in an animal in need thereof; a method for treating hypogonadism and related conditions such as osteoporosis, sexual dysfunction and weight loss in an animal in need thereof; a method for increasing muscle mass in an animal in need thereof; and a method of inducing contraception in a male animal in need thereof; comprising administering to the animal an effective amount of a compound of the invention.

One of the potential side-effects of giving testosterone orally is its first pass biological effect on the liver. The compounds of the present invention reduce the potential for such effects. Testosterone-17 β -glycoside is absorbed through the intestine and enters the portal circulation. Then, it is deposited into the systemic circulation as unmetabolised testosterone glycosides. The β -glycosidases in the body remove the β -glycoside to release free testosterone resulting in a biological effect on the target tissues.

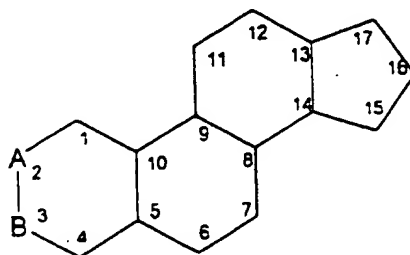
The steroid ring system numbering is in accordance with IUPAC rules. Moreover, the valence of any given carbon in Formula III will always be 4.

The invention also provides pharmaceutical compositions comprising a compound of the present invention and a pharmaceutically acceptable carrier therefor.

It will be appreciated that the term "androgen" is well known and recognised in the art, and generally relates to any compound having an effect similar to testosterone in the mammalian, especially human, system. In particular, a compound may be considered to be an androgen if it can be used in replacement therapy in, for example, male hypogonadal disorders and other situations in which testosterone is otherwise indicated.

Preferred androgens which may be glycosylated include; boldenone, clostebol, drostanolone, epitiostanol, formebolone, mepitiothane, mesterolone, methenolone, nandrolone, oxabolone, prasterone, quinbolone, stanolone, testosterone, and trenbolone. The present invention also envisages the use of such compounds as danazol, ethyloestrenol, fluoxymesterone, furazabol, methandienone, methyltestosterone, norethandrolone, oxandrolone, oxymetholone, stanozolol. These latter compounds are 17 α -alkylated compounds, and may occasionally be associated with hepatotoxicity, but it will be appreciated that any compound which serves as an androgen and which is approved for therapeutic administration may be employed in the present invention.

Glycosylation of the compounds of the present invention may be at any suitable point, but is preferably at either the 3- or 17- position. The general structure of the core of compounds of the present invention is as set out below:



It will be appreciated that this structure is based on the cholesterol system, and any reference to ring numbering herein is with reference to the above structure.

In general, any form of glycosylation may be employed, provided that it is substantially non-toxic to the patient. Many suitable glycosidic moieties are known and preferred glycosidic moieties include the glucosides and orthoesters thereof, examples of which are given below.

More generally, the methods and compounds of the invention encompass glycosides and orthoester glycosides of steroids having androgenic activity such as those disclosed in the following U.S. patents: 3,862,193; 3,917,831; 3,944,576; 3,966,713; 3,983,144; 4,220,599;

4,292,251; 4,329,296; 5,486,511; 5,545,634; 5,629,303; 5,753,639; 5,795,883; 5,855,905;
and 5,872,114.

The invention is related in particular to the discovery that compounds of the invention can be used to treat or prevent the various conditions described herein.

In preferred embodiments, R_1 is hydrogen, methyl, ethyl, ethynyl, or R_1 and R_2 together with the atoms to which they are attached, form a carbonyl group; R_2 is methyl; R_3 is hydrogen or hydroxy; R_4 is hydrogen or fluorine; R_5 is nothing, hydrogen or methyl; R_6 is hydrogen or methyl; A is oxygen, $=CH$, $C=CHOH$ or CH_2 ; B is carbonyl, CH_2 , $=CH$, or $CHOH$; R_{14} is hydrogen or methyl; or A and B together form an [2,3-d]isoxazole or a [3,2-c]pyrazole; double bonds, whenever they are present, may be at the 1,2; 4,5; 5,6; 9,10; 11,12; or at the 5,10 positions on the steroid ring; and C and D represent glycopyranosyl rings.

In other preferred embodiments, R_1 , R_3 , R_4 and R_6 are hydrogen, R_2 and R_5 are methyl, A is methinyl and B is a carbonyl; R_1 , R_3 , R_4 and R_6 are hydrogen, R_2 and R_5 are methyl, A is methinyl and B is $CHOH$; R_1 , R_2 and R_5 are methyl, R_3 , R_4 and R_6 are hydrogen, A is methinyl and B is a carbonyl; R_1 is ethyl, R_2 is methyl, R_3 , R_4 , R_5 and R_6 are hydrogen and A and B are methinyl; R_1 , R_2 and R_5 are methyl, R_3 is a hydroxy group, R_4 is fluorine, R_6 is hydrogen, A is methinyl and B is a carbonyl; R_1 , R_2 and R_5 are methyl, R_3 , R_4 and R_6 are hydrogen and A and B form a pyrazole ring; R_1 , R_3 , R_4 , R_5 and R_6 are hydrogen, R_2 is methyl, A is methinyl and B is a carbonyl; R_1 , R_2 and R_5 are methyl, R_3 , R_4 and R_6 are hydrogen, A is methinyl and B is $CHOH$; R_1 and R_2 are methyl, R_3 and R_6 are hydrogen, R_5 and R_4 are nothing, A is methinyl, B is a carbonyl group and there is a double bond between positions 9 and 10 of the steroid ring; R_1 , R_2 and R_6 are methyl, R_3 , R_4 and R_5 are hydrogen, A is methinyl and B is a carbonyl group; R_1 is ethyl, R_2 is methyl, R_3 , R_4 , R_5 and R_6 are hydrogen, A is methinyl and B is a carbonyl group; R_1 is an ethynyl group, R_2 and R_5 are methyl, R_3 , R_4 and R_6 are hydrogen and A and B form an isoxazole group; R_1 , R_2 and R_5 are methyl, R_3 , R_4 and R_6 are hydrogen, A is oxygen and B is a carbonyl group; R_1 is an acetyl group, R_2 and R_5 are methyl, R_3 , R_4 and R_6 are hydrogen, A is CHR_{13} wherein R_{13} is methyl and B is a carbonyl group; R_1 , R_3 , R_4 and R_6 are hydrogen, R_2 and R_5 are methyl, A is CHR_{13} wherein R_{13} is methyl and B is a carbonyl group; R_3 , R_4 , and R_6 are hydrogen, R_2 and R_5 are methyl, there is

a carbonyl at the 17-position of the steroid ring, A is CHR_{13} wherein R_{13} is hydrogen, B is CHOH and there is a double bond between positions 5 and 6 of the steroid ring; or R , R_1 , R_3 , R_4 , and R_6 are hydrogen, R_2 and R_5 are methyl, A is CHR_{13} wherein R_{13} is hydrogen and B is a carbonyl group. It will be appreciated that the present invention contemplates each of the above preferred embodiments individually. This also applies to any lists or groups indicated as being preferred in any manner herein.

Preferred compounds have a double bond between positions 4 and 5 or positions 5 and 6 of the steroid ring and single bonds in all other steroid ring positions.

Preferred compounds include, but are not limited to, testosterone-17 β -glucoside, 4-androstenediol-17 β -glucoside, 5 α -dihydrotestosterone-17 β -glucoside, methyltestosterone-17 β -glucoside, ethylestrenol-17 β -glucoside, fluoxymesterone-17 β -glucoside, stanozolol-17 β -glucoside, nandrolone-17 β -glucoside, methandriol-17 β -glucoside, methyltrienolone-17 β -glucoside, dimethyl-19-nortestosterone-17 β -glucoside, norethandrolone-17 β -glucoside, danazol-17 β -glucoside, oxandrolone-17 β -glucoside, oxymetholone-17 β -glucoside, methandrostenolone-17 β -glucoside, mibolerone-17 β -glucoside, boldenone-17 β -glucoside, methenolone-17 β -glucoside, tibolone-17 β -glucoside, stanolone-17 β -glucoside, prasterone-3 β -glucoside, and esters, especially orthoesters, thereof. As noted above, the present invention contemplates each of the above listing individually.

Any animal which may benefit from androgen glycosides, *e.g.*, those which have experienced or are susceptible to androgen deficiency and hypogonadism and related conditions such as osteoporosis, sexual dysfunction and weight loss, and those which have experienced or are susceptible to a decrease in muscle mass, may be treated according to the present invention. Preferred animals are humans, in particular, elderly men and women and human patients suffering from AIDS and other debilitating diseases. The phrase "debilitating diseases" is intended to encompass diseases that result in a loss or lack of strength. Upon administration of the compounds of the present invention, it is possible to reverse the adverse consequences of low muscle mass, and arrest and/or reverse the further deterioration of muscle tissue.

The compounds defined herein may also be administered to male animals as a contraceptive. In a preferred embodiment, the compounds may be combined with, and/or coadministered together with a progestational compound such as progesterone [*c.f.* Zhengwei, Y *et al.*, *Fert. Steril.* 69:89-95 (1998); Merigiola, M. C. *et al.*, *Fert. Steril.* 68:844-850 (1997); and Wu, F. C. W. *et al.*, *J. Clin. Endocrin. Met.* 84:112-122 (1999) for related methods with testosterone and derivatives thereof]. Thus, the compounds of the invention may be administered together with the progestational compound either as separate dosage forms or as a unitary pharmaceutical composition.

By glycosidic units are meant glycopyranosyl or glycofuranosyl, as well as their amino sugar derivatives. The residues may be homopolymers, random or alternating, or block copolymers thereof. The glycosidic units have free hydroxy groups which may optionally be esterified, such as by acylation with a group $R_{12}-(C=O)-$, wherein R_{12} is hydrogen, C_{1-6} alkyl, C_{6-10} substituted or unsubstituted aryl or C_{7-16} aralkyl. Preferably, the acyl groups are acetyl or propionyl. Other preferred R_{12} groups are phenyl, nitrophenyl, halophenyl, lower alkyl substituted phenyl, lower alkoxy substituted phenyl and the like or benzyl, lower alkoxy substituted benzyl and the like.

The compounds useful in the practice of the invention contain at least one glycoside or orthoester glycoside residue, preferably at position 3 or 17. Preferably, the glycoside or orthoester glycoside is linked through the 1-carbon to the 17-position on testosterone and stanolone based molecules, and to the 3-position of prasterone based molecules.

The glycoside can comprise up to, and including, 20 glycosidic units. Preferred, however, are those having less than 10, while most preferred are those having 3 or less glycosidic units. Specific examples are those containing 1 or 2 glycosidic units in the glycoside residue.

In general, the fully or partially esterified glycoside is useful as a defined intermediate in the synthesis of the deacylated material.

Among the preferred possible glycopyranosyl structures are glucose, mannose, galactose, gulose, allose, altrose, idose, or talose. Preferred furanosyl structures are derived from fructose, arabinose or xylose. Among preferred diglycosides are sucrose, cellobiose, maltose, lactose, trehalose, gentiobiose, and melibiose. Preferred triglycosides include raffinose and gentianose. The preferred amino derivatives are N-acetyl-D-galactosamine, N-acetyl-D-glucosamine, N-acetyl-D-mannosamine, N-acetylneuraminic acid, D-glucosamine, lyxosylamine, D-galactosamine, and the like.

When more than one glycosidic unit is present on a single hydroxy group, *i.e.*, di- or polyglycosidic residues, the individual glycosidic rings may be bonded by 1-1, 1-2, 1-3, 1-4, 1-5 or 1-6 bonds, most preferably 1-2, 1-4 and 1-6. The linkages between individual glycosidic rings may be α or β .

The water soluble glycosidic derivatives of the aforementioned compounds may be obtained according to the general methods disclosed by Holick in US-A- 4,410,515, the contents of which are fully incorporated by reference herein. The glycosyl orthoester compounds may be obtained according to US-A-4,521,410, the contents of which are fully incorporated by reference herein. Preferred testosterone glycosyl orthoesters are testosterone-17 β -(α 1-D-glucopyranosyl-1',2'-orthoacetate) and testosterone-17- β -1-glucopyranosyl-1',2'-orthoacetate.

The compounds of the invention may be administered in any appropriate pharmaceutically acceptable carrier for oral administration since the testosterone glycosides and derivatives thereof are biologically active upon oral administration, which is the preferred route. The compounds of the invention may also be administered in any appropriate pharmaceutical carrier for parenteral, intramuscular or topical administration. They can be administered by any means that treat androgen deficiency and hypogonadism and related conditions such as osteoporosis, sexual dysfunction and weight loss, treat or prevent decreased muscle mass or increase muscle mass, especially in elderly humans or patients suffering from muscle debilitation, AIDS or any debilitating disease. In addition, the compounds of the present invention can be administered by any means whereby the compounds function as male contraceptives.

The dosage administered will depend on the age, health and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. An exemplary systemic daily dosage is about 0.001 to about 100.0 mg/kg of body weight. Normally, from about 0.01 to about 10.0 mg/kg of body weight of the glycoside or orthoester glycoside, in one or more dosages per day, is effective to obtain the desired results. One of ordinary skill in the art can determine the optimal dosages and concentrations of other active testosterone compounds and orthoester glycoside compounds with only routine experimentation.

The compounds may be employed in dosage forms such as tablets, capsules or powder packets, or liquid solutions, suspensions or elixirs for oral administration, as well as sterile liquid for formulations such as solutions or suspensions for parenteral use. A lipid vehicle can be used in parenteral administration. The compounds could also be administered *via* topical patches, ointments, gels or other transdermal applications. In such compositions, the active ingredient will ordinarily be present in an amount of at least 0.1% by weight based on the total weight of the composition, and not more than 90% by weight. An inert pharmaceutically acceptable carrier is preferable such as 95% ethanol, vegetable oils, propylene glycols, saline buffers, sesame oil, *etc.* Reference is made to *Remington's Pharmaceutical Sciences*, 18th Edition, Gennaro *et al.* (eds.), 1990, for methods of preparing pharmaceutical compositions.

The invention also relates to pharmaceutical combinations comprising a compound of the invention together with a progestational compound such as progesterone, wherein each compound is present in an amount effective to induce contraception in a male animal. Such pharmaceutical compositions may also comprise a pharmaceutically acceptable carrier as described herein.

The compounds administered are preferably substantially pure, by which is meant the compounds are created by chemical synthesis and/or are substantially free of chemicals which may accompany the compounds in the natural state, as evidenced by thin layer chromatography (TLC) or high performance liquid chromatography (HPLC) (see Example 3).

It should be noted that some compounds of the present invention may exist as keto/enol isomers. Moreover, some of the compounds may exist as stereoisomers including optical isomers. The invention includes all stereoisomers and both the racemic mixtures of such stereoisomers as well as the individual enantiomers that may be separated according to methods that are well known to those of ordinary skill in the art.

The present invention will now be further illustrated by the following Examples which are for purposes of illustration only and are not intended to be limiting unless otherwise specified. All patents, patent applications and publications cited herein are incorporated by reference in their entirety.

EXAMPLE 1

Organic Synthesis of Testosterone-glucoside

The synthetic sequence starts from testosterone which is commercially available from Sigma Chemical Co., St. Louis, MO (T-1500). 4-Androsten-17- β -ol-3-one is the IUPAC name for testosterone (CAS # 58-22-0). Acetobromo- α -D-glucose; the bromo sugar used in the conjugation is commercially available through Sigma Chemical Co. (A-1750). The IUPAC name for acetobromo- α -D-glucose is 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide (CAS # 572-09-8). Cadmium salts were obtained from Aldrich Chemical Co. Inc., Milwaukee, WI, and used without further purification. Silver fluoride and silver nitrate were purchased from Aldrich Chemical Co., Inc., and used without further purification. Hydrated sodium metasilicate, valerolactone and maleic anhydride were also purchased from Aldrich and used without further purification for the synthesis of silver silicate and silver salts of carboxylic acids. Silver silicate for the conjugation of acetobromo- α -D-glucose was prepared from silver fluoride and sodium metasilicate. Silver nitrate was used in the preparation of silver carboxylates either by the exchange of sodium anion of the carboxylate or the lanthanide salts preferably uranium carboxylates for silver anion. The silver salts were prepared freshly and dried before use.

The synthetic sequence involves conjugating testosterone with acetobromo- α -D-glucose with salts like cadmium carbonate or cadmium acetate in inert solvents like benzene, toluene or xylene wherein the starting materials and products were soluble while hot. The reactions of silver salts were performed near room temperature in chlorinated organic solvents like dichloromethane, ether or acetonitrile.

EXAMPLE 2

Testosterone-17- β -(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranose)
(Testosterone-glucoside tetra-acetate)

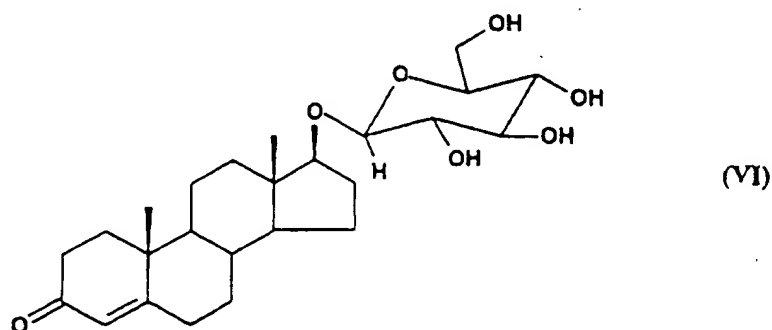
Testosterone (2.3 g; 8 mmol) and acetobromo- α -D-glucose (3.94 g; 9.6 mmol) were added to a suspension of cadmium carbonate (2.06 g) in xylene (100 ml). The suspension was heated to reflux and stirred under an inert atmosphere for about 5 hours during which time the reaction was essentially complete. The progress of the reaction was monitored by reverse-phase TLC plates. The reaction gave a blue tinge to the cadmium surface. The reaction mixture was evaporated to remove xylenes under reduced pressure and chromatographed on silica gel and eluted with ethyl acetate and hexane resulting in the titled tetra-acetate as a crystalline solid (1.1 g, from diethylether). Testosterone (1 g) was reclaimed and used in subsequent reactions without any purification.

EXAMPLE 3

Testosterone-17- β -1'- β '-D-glucopyranose: Testosterone glucoside

A mixture of testosterone (5.76 g; 20 mmol) and acetobromo- α -D-glucose (9.86 g; 24 mmol) was added to freshly prepared dry cadmium acetate (from 5.4 g of dihydrate; 20 mmol) suspended in dry benzene (85 ml). The mixture was refluxed for 3 hours during which time it was found that the reaction was essentially complete. There was a distinct purplish tinge to the cadmium surface during the onset of the reaction. Testosterone (3.2 g) and testosterone tetra-acetate (2.6 g) were obtained as white solids after chromatography.

1 g of tetra-acetate of testosterone-glucoside was dissolved in 80 ml of methanol and 4 g of Dowex 550A-OH resin were added. The stirred suspension was heated to reflux for 4 hours during which time the reaction was completed. The product was isolated by filtering off the resin, evaporating off the solvents and crystallising the crude gum from ethyl acetate giving 800 mg of white crystals.



Testosterone-17-β-1'-β'-D-glucopyranose

Spectral Data

NMR spectrum of tetra-acetate of testosterone-β-glucoside:

δ 0.9 (singlet, 3H, 18 angular methyl);

δ 1.1 (singlet, 3H, angular methyl);

four overlapping singlets centred at δ 2.0 (acetate methyl groups);

multiplet δ 2.5-0.9 (20 H; CH₂ and CH protons);

δ 5.7 (singlet; 1H, enone);

δ 5.25 to 4.9 (three overlapping triplets 3H; coupling constant 10 hertz);

δ 4.5 (1H; doublet, coupling constant 10.2 hertz; signifying a beta glucosidic linkage);

δ 3.2-4.25 (4H; 3 protons from the sugar residue and 1H from 17 position).

NMR spectrum of testosterone 17- β -glucoside:

δ 0.9 (singlet, 3H, C18 methyl);

δ 1.1 (singlet, 3H, angular methyl);

δ 0.91-2.5 (complex multiplets for 20H, CH₂ and CH protons);

δ 5.8 (singlet, 1H, enone);

δ 4.3 (doublet, coupling constant 9.8 hertz, 1H, anomeric sugar hydrogen);

δ 3.2-3.9 (multiplets, 7H, 1 proton from 17 position of the steroid and rest from sugar).

Mass spectrum:

sodium ion bombardment gave a molecular ion at 473.27, *i.e.*, corresponding to molecular weight of 450.27, which agrees with the structure.

HPLC analysis:

reverse phase HPLC using a C18 column gave a single peak. Retention time 5.04 using water : methanol mixture (2 : 1).

EXAMPLE 4

17- β -O-[1'- β '-glucopyranosyl]-3-androsterone: Stanolone glucoside

A mixture of cadmium carbonate (6 g), stanolone (2 g) and acetobromo- α -D-glucose (6.8 g), as a slurry in dry toluene (80 ml), was heated to reflux under argon. The moisture in the starting materials was azeotroped off using a Dean-Stark apparatus. The mixture was refluxed for 5 hours more. TLC examination showed the reaction was complete (2 % copper sulphate solution in 10 % sulphuric acid was used to stain). The reaction mixture was cooled and subjected to silica gel column chromatography. Stanolone glucoside tetraacetate (17- β -O-[1'- β '-2',3',4',6'-tetra-O-acetyl glucopyranosyl]-3-androstanone) was obtained as a gummy solid. Dry diethyl ether was added and the product crystallised out as a white solid (2.4 g).

Stanolone glucoside tetraacetate (1.8 g) and Dowex-110 OH resin (5.8 g) in methanol (60 ml) was refluxed under argon for 6 hours. The mixture was filtered while hot and the solvent was evaporated. The product crystallised as a hard solid. It was powdered and washed with 50% ethyl acetate-ether mixture. The solid was collected and dried. The product, stanolone glucoside (17- β -O-[1'- β '- glucopyranosyl]-3-androstanone), weighed 850 mg and it was found to be homogeneous by spectroscopic means.

Spectral Data

NMR spectrum of stanolone glucoside tetraacetate : (CDCl₃)

δ 5.3 to 3.5 (8H, sugar-H and C17-H),
 δ 1.9 to 2.1 (overlapping singlets, 12H, acetates),
 δ 2.4 to 0.8 (multiplets, aliphatic H, 22H),
 δ 1.0 (singlet, 3H, methyl) and
 δ 0.7 (singlet, 3H, C18-CH₃)

Mass Spectrum:

molecular ion with Na⁺ at 643.3 amu corresponding to 620.3 amu. The theoretical value expected is 620.3 amu.

NMR spectrum of stanolone glucoside : In deuterated dimethyl sulphoxide.

δ 0.7 (singlet, 3H, CH₃),
 δ 0.9 (singlet, 3H, CH₃),
 δ 4.1 (doublet, anomeric coupling 8 Hz, 1H, β -linkage),
 δ 0.75 to 2.5 (multiplets, aliphatic H, 22H),
 δ 2.8 to 4.7 (multiplets, sugar-H and C17-H, 7H).

Mass Spectrum:

molecular ion with Na⁺ at 475.4 amu which corresponds to 452.4 amu was obtained. The theoretical value expected is 475.4 amu

EXAMPLE 5***5-Androsten-3- β -O-(1'- β '- glucopyranosyl)-17-one: Prasterone glucoside***

A mixture of dehydroisoandrosterone (5.0 g), cadmium carbonate (13.8 g) and acetobromo- α -D-glucose (13.0 g) in toluene (200 ml) was heated to reflux under argon. The moisture from the reactants was removed using by Dean-Stark apparatus. The mixture was refluxed for an additional 5 hours. TLC examination revealed that the reaction was essentially complete. The product, as a slurry, was separated by silica gel column chromatography. The product, prasterone glucoside tetraacetate [5-androsten-3- β -O-(1'- β '-2',3',4',6'-tetra-O-acetyl)-gluco-pyranosyl-17-one) was obtained as a crystalline solid (5.9 g).

A mixture of prasterone glucoside tetraacetate (2.0 g) in methanol (60 ml) and Dowex-110-OH resin (6 g) was refluxed under argon for 8 hours. The mixture was filtered while hot and evaporated to dryness. Triturating the solid with 50 % ethyl acetate-ether mixture left a white solid. The solid was filtered and washed with ether to afford 670 mg of pure prasterone glucoside (5-androsten-3- β -O-(1'- β '- glucopyranosyl)-17-one).

Spectral Data**NMR spectrum of prasterone glucoside tetraacetate:**

δ 4.52 (doublet, 7.5 Hz, anomeric-H, β -linkage),
 δ 5.4-3.4 (multiplets, sugar-H, and C3-H, and C6-vinylic-H, 9H), and
 δ 0.8 and 1.0 (two singlets, CH₃, 6H),
 δ 2.0 to 2.1 (four overlapping singlets, acetates, 12H) and
 δ 1.0 to 2.5 (multiplets, aliphatic-H, 19H).

Mass Spectrum:

molecular ion with Na⁺ at 641.4 which corresponds to 618.4 amu was obtained. The theoretical value expected is 618.5 amu.

NMR spectrum of prasterone glucoside: (*d*₆-DMSO)

δ 0.8 and 0.95 (two singlets, CH₃, 6H),

δ 1.0 to 2.4 (multiplets, aliphatic-H, 19H),

δ 2.7 to 4.3 (multiplets, 8H, sugar-H and C3-H, and anomeric-H is a doublet, 8 Hz, at δ 4.2)

and δ 5.3 (broad singlet, vinylic-H, 1H).

Mass Spectrum:

molecular ion with Na^+ at 473.2 which corresponds to 450.2 amu was obtained. The theoretical value expected is 450.4 amu.

EXAMPLE 6

Testosterone-17- β -1'- β' -D-glucopyranose: Testosterone glucoside

Testosterone (1.15g; 4 mmol) and acetobromo- α -D-glucose (1.97g; 4.8 mmol) were added to a suspension of silver silicate (4g; excess) in dichloromethane (50mL). The reaction mixture was stirred for a period of 5 hours at room temperature and during this period all the testosterone was consumed. After the removal of the solids and evaporation of the solvent, the product was used as such in the deacetylation as in Example 3. The product from the deacetylation was recrystallised from ethyl acetate to afford 900 mg of the desired beta-glucosylated testosterone. The spectral characteristics of the compounds isolated in these experiments were identical to the compounds described in Examples 2 and 3.

EXAMPLE 7

5-Androsten-3- β -O-(1'- β' - glucopyranosyl)-17- one: Prasterone glucoside

A mixture of dehydroisoandrosterone (1g) and silver silicate (2.5g) in dichloromethane (50mL) was stirred at 0° C. Acetobromo- α -D-glucose (2g) was added and the mixture was warmed to room temperature. After 3 hours the product was isolated after removing the silver salts and evaporation of the solvent. Prasterone glucoside tetra acetate

was isolated almost in quantitative yield. The spectral data are identical to those of the compound described in Example 5.

EXAMPLE 8

Study to Determine the Ability of Testosterone-glucoside to Increase Serum Testosterone in Orchiectomised Rats

Experimental Procedure

1. Fifteen 200 g Sprague-Dawley male rats were orchiectomised and allowed to recover for 1 week at Charles River Laboratories.
2. Rats were shipped to the Laboratory Animal Science Center at the Boston University School of Medicine, randomised, coded, weighed, and housed individually in cages for 24 hours with food and water *ad libitum*.

Animal Test Groups:

C = control

T_{IM} = intramuscularly injected testosterone

T_O = orally administered testosterone

G_{IM} = intramuscularly injected testosterone-glucoside

G_O = orally administered testosterone-glucoside

3. Rats were anaesthetised with ketamine and 1.5 ml of blood was removed from each animal by tail snip and the wounds were cauterised with silver nitrate.
4. Blood samples were spun to separate serum which was pipetted into new tubes and frozen at -70°C.

5. Animals were dosed daily for 6 days with 1 mg testosterone or a molar equivalent (1.56 mg) of testosterone-glucoside in 100 μ l of 25% EtOH/propylene glycol by intramuscular injection or oral administration.
6. Four hours after the final dose, the rats were anaesthetised with ketamine and 5 ml of blood was removed from each animal by cardiopuncture and the carcasses sent for incineration.
7. Blood samples were spun to separate serum which was pipetted into new tubes and frozen at -70°C .

Analytical Procedure

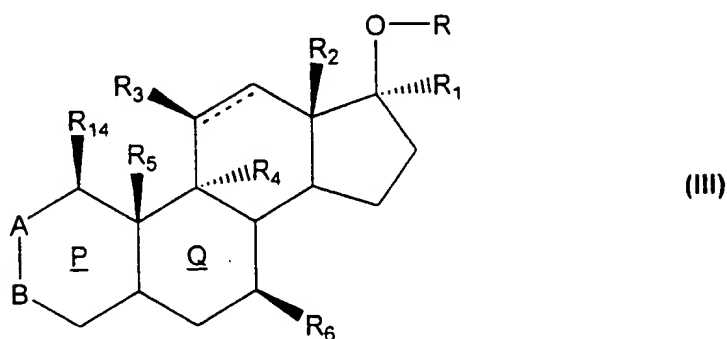
1. Serum samples were thawed in an ice bath and 50 μ l aliquots were transferred to 12 x 75 mm borosilicate test tubes in triplicate.
2. Aliquoted samples were applied to a testosterone radio-immunoassay (Diagnostic Systems Laboratories; Webster, Texas) to determine serum testosterone concentrations.
3. Average serum testosterone values for each animal were determined and statistical analysis was performed on each test group to calculate means and standard deviations. These calculated values are shown in Figure 1.

Figure 1 is a bar graph showing the effects of injected and orally administered testosterone and testosterone-glucoside on serum testosterone levels in orchiectomised male rats. As described above, orchiectomised male rats (3 animals per group) were given 1 mg of testosterone (Test) or a molar equivalent (1.56 mg) of testosterone-glucoside (TG) in 100 μ l of 25% EtOH/propylene glycol by intramuscular injection (IM) or oral administration daily for 6 days. Blood samples were taken 4 hours after the final dose. Serum testosterone levels were determined for each group by testosterone radio-immunoassay. The bars represent the mean serum testosterone levels \pm standard deviation for each group. * Denotes $p < 0.001$ versus control animals.

The animals that received oral testosterone had lower blood levels of testosterone than the animals that received testosterone glucoside, orally and intramuscularly. The results demonstrate that testosterone glucoside is bioavailable when given orally, as well as intramuscularly, and is readily metabolised to testosterone.

Claims:

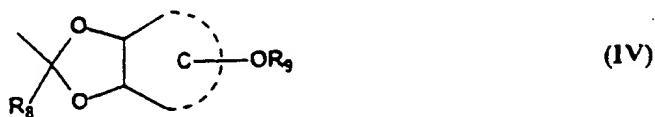
1. An androgen glycoside, other than testosterone-17- β -1'- β '-D-glucopyranose.
2. A compound having the Formula (III):



wherein the dotted line represents a single or double bond;

the rings P and Q are, independently, saturated or partially unsaturated;

R is hydrogen or a straight or branched chain glycosidic residue containing 1 - 20 glycosidic units per residue, or R is an orthoester glycoside moiety of the Formula (IV):



wherein the semi-dotted ring indicated at "C" is a glycofuranosyl or glycopyranosyl ring;

R₈ is hydrogen; C₁₋₄ alkyl; C₇₋₁₀ aralkyl; phenyl; phenyl substituted by chloro, fluoro, bromo, iodo, C₁₋₄ alkyl or C₁₋₄ alkoxy; or is naphthyl;

R₉ is hydrogen or a straight or branched chain glycosidic residue containing 1 - 20 glycoside units;

R₁ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkanoyl or R₁ and R, together with the atoms to which they are attached, form a carbonyl group;

R₂ is hydrogen or C₁₋₄ alkyl;

R₃ is hydrogen or hydroxy;

R₄, where present, is hydrogen or a halogen atom;

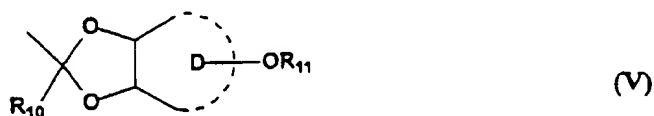
R₅, where present, is hydrogen or C₁₋₄ alkyl;

R₆ is hydrogen or C₁₋₄ alkyl;

R₁₄ is hydrogen or C₁₋₄ alkyl;

A is oxygen, $\equiv\text{CH}$, $>\text{C}=\text{CHOH}$, or is the group $>\text{CHR}_{13}$, wherein R₁₃ is hydrogen or a C₁₋₄ alkyl group, or A and B together form an optionally substituted pyrazole or isoxazole ring;

B is a carbonyl group, $\equiv\text{CH}$, $>\text{CH}_2$, $>\text{CHOR}_7$ or $=\text{C}(\text{OR}_7)-$, wherein R₇ is hydrogen or a straight or branched chain glycosidic residue containing 1 - 20 glycoside units, or R₇ is an orthoester glycoside moiety of the Formula (V):



wherein the semi-dotted ring indicated at "D" represents a glycofuranosyl or glycopyranosyl ring;

R₁₀ is hydrogen; C₁₋₄ alkyl; C₇₋₁₀ aralkyl; phenyl; phenyl substituted by chloro, fluoro, bromo, iodo, C₁₋₄ alkyl or C₁₋₄ alkoxy; or is naphthyl; and

R₁₁ is hydrogen or a straight or branched chain glycosidic residue containing 1 - 20 glycoside units;

and esters thereof;

provided that the compound is not an unsubstituted glucoside of testosterone, 5 α -androstan-3 β ,17 β -diol or epiandrosterone, and that, when R is hydrogen, then B is $>\text{CHOR}_7$ or $=\text{C}(\text{OR}_7)-$, and R₇ is a glycosidic residue or orthoester glycoside moiety.

3. A compound according to claim 2, wherein A and B together form a [2,3-d]isoxazole or a [3,2-c]pyrazole ring.

4. A compound according to claim 2 or 3, wherein C and D represent glycopyranosyl rings.

5. A compound according to any of claims 2 to 4, wherein R_{13} is not hydrogen.
6. A compound according to any preceding claim, which compound is an orthoester glycoside.
7. A compound according to any preceding claim, wherein at least one glycosidic residue is acylated.
8. A compound according to claim 7, wherein the acyl substituent is a group $R_{12}-(C=O)-$, wherein R_{12} is hydrogen, C_{1-6} alkyl, C_{6-10} substituted or unsubstituted aryl or is C_{7-16} aralkyl.
9. A compound according to claim 8, wherein R_{12} is methyl.
10. A compound according to any of claims 2 to 9, wherein R_1 , R_3 , R_{14} , R_4 and R_6 are hydrogen, R_2 and R_5 are methyl, A is methinyl and B is a carbonyl.
11. A compound according to any of claims 2 to 9, wherein R_1 , R_2 and R_5 are methyl, R_3 , R_{14} , R_4 and R_6 are hydrogen, A is methinyl and B is a carbonyl.
12. A compound according to any of claims 2 to 9, wherein R_1 is ethyl, R_2 is methyl, A and B are methinyl and R_3 , R_4 , R_{14} , R_5 and R_6 are hydrogen.
13. A compound according to any of claims 2 to 9, wherein R_1 , R_2 and R_5 are methyl, R_3 is a hydroxy group, R_4 is fluorine, R_6 and R_{14} are hydrogen, A is methinyl and B is a carbonyl.
14. A compound according to any of claims 2 to 9, wherein R_1 , R_2 and R_5 are methyl, R_3 , R_{14} , R_4 and R_6 are hydrogen and A and B form a pyrazole ring.
15. A compound according to any of claims 2 to 9, wherein R_1 , R_3 , R_4 , R_{14} , R_5 and R_6 are hydrogen, R_2 is methyl, A is methinyl and B is a carbonyl.

16. A compound according to any of claims 2 to 9, wherein R_1 , R_2 and R_5 are methyl, R_3 , R_{14} , R_4 and R_6 are hydrogen, A is methinyl and B is CHOH.
17. A compound according to any of claims 2 to 9, wherein R_1 and R_2 are methyl, R_3 , R_{14} , R_4 and R_6 are hydrogen, R_5 is nothing, A is methinyl, B is a carbonyl group and there is a double bond between positions 9 and 10 of the steroid ring.
18. A compound according to any of claims 2 to 9, wherein R_1 , R_2 and R_6 are methyl, R_3 , R_{14} , R_4 and R_5 are hydrogen, A is methinyl and B is a carbonyl group.
19. A compound according to any of claims 2 to 9, wherein R_1 is ethyl, R_2 is methyl, R_3 , R_4 , R_{14} , R_5 and R_6 are hydrogen, A is methinyl and B is a carbonyl group.
20. A compound according to any of claims 2 to 9, wherein R_1 is an ethynyl group, R_2 and R_5 are methyl, R_3 , R_{14} , R_4 and R_6 are hydrogen and A and B form an isoxazole group.
21. A compound according to any of claims 2 to 9, wherein R_1 , R_2 and R_5 are methyl, R_3 , R_{14} , R_4 and R_6 are hydrogen, A is oxygen and B is a carbonyl group.
22. A compound according to any of claims 2 to 9, wherein R_1 , R_2 and R_5 are methyl, R_3 , R_{14} , R_4 and R_6 are hydrogen, A is $C=CHOH$ and B is a carbonyl group.
23. A compound according to any of claims 2 to 9, wherein R_1 , R_3 , R_4 , R_{14} , R_5 and R_6 are hydrogen, R_2 and R_5 are methyl, A is methinyl and B is a carbonyl group.
24. A compound according to any of claims 2 to 9, wherein R_1 , R_3 , R_{14} , R_4 and R_6 are hydrogen, R_2 and R_5 are methyl, A is methinyl and B is CHOH.
25. A compound according to any of claims 2 to 9, wherein R_1 is an acetyl group, R_2 and R_5 are methyl, R_3 , R_{14} , R_4 and R_6 are hydrogen, A is CHR_{13} wherein R_{13} is methyl and B is a carbonyl group.

26. A compound according to any of claims 2 to 9, wherein R_1 , R_3 , R_{14} , R_4 and R_6 are hydrogen, R_2 and R_5 are methyl, A is CHR_{13} wherein R_{13} is methyl and B is a carbonyl group.
27. A compound according to any of claims 2 to 9, wherein R , R_1 , R_3 , R_4 , R_{14} and R_6 are hydrogen, R_2 and R_5 are methyl, A is CHR_{13} wherein R_{13} is hydrogen and B is a carbonyl group.
28. A compound according to any of claims 2 to 9, wherein there is a carbonyl group at the 17-position of the steroid ring structure.
29. A compound according to any of claims 2 to 9, wherein R_3 , R_4 , R_{14} and R_6 are hydrogen, R_2 and R_5 are methyl, there is a carbonyl at the 17-position of the steroid ring, A is CHR_{13} wherein R_{13} is hydrogen, B is $CHOH$ and there is a double bond between positions 5 and 6 of the steroid ring.
30. A compound according to any of claims 1 to 9, wherein the compound is 5α -dihydrotestosterone-17 β -glucoside, methyltestosterone-17 β -glucoside, ethylestrenol-17 β -glucoside, fluoxymesterone-17 β -glucoside, stanozolol-17 β -glucoside, nandrolone-17 β -glucoside, methandriol-17 β -glucoside, methyltrienolone-17 β -glucoside, dimethyl-19-nortestosterone-17 β -glucoside, norethandrolone-17 β -glucoside, danazol-17 β -glucoside, oxandrolone-17 β -glucoside, oxymetholone-17 β -glucoside, methandrostenolone-17 β -glucoside, mibolerone-17 β -glucoside, boldenone-17 β -glucoside, 4-androstenediol-17 β -glucoside, methenolone-17 β -glucoside, tibolone-17 β -glucoside, stanolone-17 β -glucoside, prasterone-3 β -glucoside, or orthoester thereof.
31. A compound according to claim 1 or 2, which is 17- β -O-(1'- β '-glucopyranosyl)-3-androsterone.
32. A compound according to claim 1 or 2, which is 5-androsten-3- β -O-(1'- β '-glucopyranosyl)-17-one.
33. An androgen glycoside for use in therapy.

34. A compound according to any of claims 1 to 32, for use in therapy.
35. Testosterone-17- β -1'- β '-D-glucopyranose for use in therapy.
36. A pharmaceutical composition comprising a compound as defined in any preceding claim, together with a pharmaceutically acceptable carrier therefor.
37. A pharmaceutical composition according to claim 36, further comprising a progestational compound.
38. Use of a compound as defined in any of claims 1 to 35 in the manufacture of a medicament for increasing muscle mass in an animal.
39. Use of a compound as defined in any of claims 1 to 35 in the manufacture of a medicament for the treatment of a hypogonadal disorder in an animal.
40. Use of a compound as defined in any of claims 1 to 35 in the manufacture of a medicament for the treatment of an androgen deficiency in an animal.
41. Use of a compound as defined in any of claims 1 to 35 in the manufacture of a medicament for the treatment of sexual dysfunction in an animal.
42. Use of a compound as defined in any of claims 1 to 35 in the manufacture of a medicament for treating osteoporosis in an animal.
43. Use of a compound as defined in any of claims 1 to 35 in the manufacture of a medicament for the treatment of a debilitating disease in an animal.
44. Use of a compound as defined in any of claims 1 to 35 in the manufacture of a medicament for treatment of a human suffering from AIDS.

45. Use of a compound as defined in any of claims 1 to 35 in the manufacture of a medicament for the treatment of a human suffering from weight loss.
46. Use of a compound as defined in any of claims 1 to 35 in the manufacture of a medicament for inhibiting conception in a male animal.
47. Use according to claim 46, wherein a compound having progestational activity is also used.
48. Use according to claim 37, wherein the compound having progestational activity is progesterone.
49. Use according to any one of claims 38 to 48, adapted to administer the compound in an amount ranging from about 0.001 to about 100.0 mg/kg body weight per day.
50. Use according to any of claims 38 to 49, wherein the medicament is for oral administration.
51. Use according to any one of claims 38 to 50, wherein the animal is a human.
52. Use according to any one of claims 38 to 50, wherein the animal is an elderly person.

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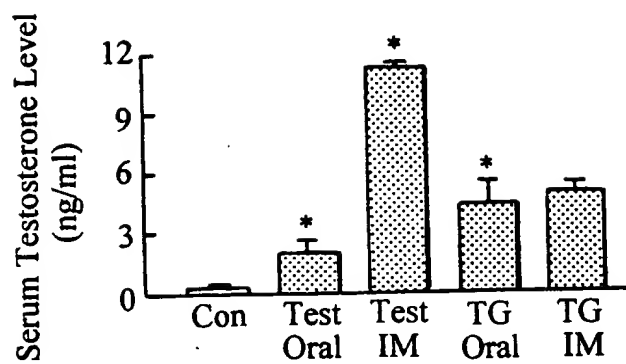


Fig. 1

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/GB 00/01700

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J17/00 A61K31/70 A61K31/58 C07J71/00 A61P5/26

According to International Patent Classification (IPC) as to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07J A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MELLOR, JOYCE D. ET AL: "Steroid.beta.-D-glucosidase activity in rabbit tissues" J. BIOL. CHEM. (1971), 246(14), 4377-80 , XP000933557	1,32
Y	the whole document	2-52
Y	VOJTISKOVA, MARTA ET AL: "Biological activity of hormonally active and nonactive androgen derivatives" INT. J. IMMUNOPHARMACOL. (1982), 4(5), 469-74 , XP000933419 cited in the application the whole document	1-52
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

1 August 2000

Date of mailing of the international search report

24/08/2000

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Authorized officer

Watchorn, P

FURTHER INFORMATION CONTINUED FROM PCT/IS// 210

Continuation of Box I.2

Claims Nos.: 1-29 (searched in part) 30-52 (searched in full)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty of the claimed compounds - in total over 100 compounds affecting the novelty of the claimed compounds. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to those compounds specifically mentioned in the examples, and specifically named in claims 30-32.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/01700

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CUNNINGHAM, G. R. ET AL: "Differences in steroid specificity for rat androgen binding protein and the cytoplasmic receptor" STEROIDS (1979), 33(3), 261-76 , XP002143251	1,2,10, 23
Y	page 270; table 8	1-52
X	TINDALL, D. J. ET AL: "Structural requirements for steroid binding to androgen binding proteins" INT. J. ANDROL., SUPPL. (1978), 2(2, ENDOCR. APPROACH MALE CONTRACEPT.), 434-48 XP000934320	1,2,10
Y	the whole document	1-52
X	CUNNINGHAM, G. R. ET AL: "Characterization of steroid binding specificity of the androgen receptor in human foreskin fibroblasts" STEROIDS (1983), 41(5), 617-26 , XP002143253	1,2,10
Y	page 621; table 1	1-52
X	GB 1 175 219 A (ICI LTD) 23 December 1969 (1969-12-23) example 2	1,2, 7-10,30
X	SCHNEIDER, JOHN JOSEPH: "Preparation and properties of some new steroid.beta.-D-glucopyranosides,.beta.-D-glucopyranosiduronic acids, and derivatives" CARBOHYD. RES. (1971), 17(1), 199-207 , XP000925710	1,2,7-9, 28,30-32
X	KOCOVSKY, P. ET AL: "Steroids. CLXI. Synthesis of some new steroid glucosides" COLLECT. CZECH. CHEM. COMMUN. (1973), 38(11), 3273-8 , XP002143255	1,2, 7-10,28
Y	page 3274, compounds XXI, XVII, XXIII, XXV, XXVI, XXVII	
Y	GB 916 778 A (FRANCESCO VISMARA S.P.A.) 30 January 1963 (1963-01-30) page 1, column 1, paragraphs 2,4 page 2, column 1, paragraph 1	1-52
Y	GB 1 338 547 A (SYNTEX CORP) 28 November 1973 (1973-11-28) the whole document	1-52

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No

PCT/GB 00/01700

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